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SERIAL NO: 10/078,949

DOCKET NO: ISIS-5027

AMENDMENTS TO THE CLAIMS: This listing of claims replaces all prior versions and listings of claims in the instant patent application.

Listing of claims:

1-164. (Canceled)

165. (New) A method of activating a double-stranded RNA nuclease, comprising contacting the nuclease with a double-stranded RNA comprising a first oligonucleotide and a second oligonucleotide, wherein:

at least one of said first and said second oligonucleotides comprise at least four consecutive 2'-hydroxyl ribonucleosides and at least one modified nucleoside;
said first and said second oligonucleotides are hybridized to each other; and
said first and said second oligonucleotides are not covalently linked.

166. (New) The method of claim 165, wherein activation of said double-stranded RNA nuclease results in cleavage of the double-stranded RNA.

167. (New) The method of claim 165, wherein the modified nucleoside or nucleosides increase resistance of said oligonucleotide to single-stranded nucleases and/or increase the affinity of said oligonucleotide to the other oligonucleotide.

168. (New) The method of claim 167, wherein at least one modification is 2'-methoxy.

169. (New) The method of claim 167, wherein at least one modification is 2'-fluoro.

170. (New) The method of claim 167, wherein at least one modification is 2'-O-(methoxyethyl).

171. (New) The method of claim 167, wherein at least one modification is a phosphorothioate internucleoside linkage.

172. (New) The method of claim 165, wherein said first oligonucleotide and said second oligonucleotide each have at least four consecutive 2'-hydroxyl ribonucleosides.

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173. (New) The method of claim 172, wherein the 2'-hydroxyl residues of said first and said second oligonucleotides have phosphodiester linkages.

174. (New) The method of claim 172, wherein the 2'-hydroxyl residues of said first and said second oligonucleotides have phosphorothioate linkages.

175. (New) The method of claim 172, wherein the 2'-hydroxyl residues of said first oligonucleotide have phosphodiester linkages and the 2'-hydroxyl residues of said second oligonucleotide have phosphorothioate linkages.

176. (New) The method of claim 172 or claim 175, wherein said first and said second oligonucleotides further comprise flanking residues 5' and 3' of the 2'-hydroxyl ribonucleosides, wherein said flanking residues have phosphorothioate linkages.

177. (New) The method of claim 176, wherein said flanking residues of at least one of said first and said second oligonucleotides further comprises 2'-methoxynucleosides.

178. (New) The method of claim 176, wherein said flanking residues of each of said first and said second oligonucleotides further comprise 2'-methoxynucleosides.

179. (New) The method of claim 165, wherein at least one of said first and said second oligonucleotides comprises at least eight consecutive 2'-hydroxyl ribonucleosides.

180. (New) The method of claim 179, wherein said first oligonucleotide and said second oligonucleotide each comprise at least eight consecutive 2'-hydroxyl ribonucleotides.

181. (New) The method of claim 165, wherein each of said first and said second oligonucleotides are about 17 to about 20 nucleoside subunits in length.

182. (New) The method of claim 181, wherein each of said first and said second oligonucleotides are 17 subunits in length.

183. (New) The method of claim 181, wherein each of said first and said second oligonucleotides are 20 subunits in length.

184. (New) A method of detecting a double-stranded RNA nuclease in a sample, comprising contacting the sample with a double-stranded RNA comprising a first

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oligonucleotide and a second oligonucleotide, wherein:

at least one of said first and said second oligonucleotides comprise at least four consecutive 2'-hydroxyl ribonucleosides and at least one modified nucleoside;
said first and said second oligonucleotides are hybridized to each other; and
said first and said second oligonucleotides are not covalently linked, wherein cleavage of the double-stranded RNA indicates the presence of a double-stranded RNA nuclease.

185. (New) The method of claim 184, wherein the modified nucleoside or nucleosides increase resistance of said oligonucleotide to single-stranded nucleases and/or increase the affinity of said oligonucleotide to the other oligonucleotide.

186. (New) The method of claim 185, wherein at least one modification is 2'-methoxy.

187. (New) The method of claim 185, wherein at least one modification is 2'-fluoro.

188. (New) The method of claim 185, wherein at least one modification is 2'-O-methoxyethyl.

189. (New) The method of claim 185, wherein at least one modification is a phosphorothioate internucleoside linkage.

190. (New) The method of claim 184, wherein said first oligonucleotide and said second oligonucleotide each have at least four consecutive 2'-hydroxyl ribonucleosides.

191. (New) The method of claim 190, wherein the 2'-hydroxyl residues of said first and said second oligonucleotides have phosphodiester linkages.

192. (New) The method of claim 190, wherein the 2'-hydroxyl residues of said first and said second oligonucleotides have phosphorothioate linkages.

193. (New) The method of claim 190, wherein the 2'-hydroxyl residues of said first oligonucleotide have phosphodiester linkages and the 2'-hydroxyl residues of said second oligonucleotide have phosphorothioate linkages.

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194. (New) The method of claim 190 or claim 193, wherein said first and said second oligonucleotides further comprise flanking residues 5' and 3' of the 2'-hydroxyl ribonucleosides, wherein said flanking residues have phosphorothioate linkages.

195. (New) The method of claim 194, wherein said flanking residues of at least one of said first and said second oligonucleotides further comprises 2'-methoxynucleosides.

196. (New) The method of claim 194, wherein said flanking residues of each of said first and said second oligonucleotides further comprise 2'-methoxynucleosides.

197. (New) The method of claim 184, wherein at least one of said first and said second oligonucleotides comprises at least eight consecutive 2'-hydroxyl ribonucleosides.

198. (New) The method of claim 197, wherein said first oligonucleotide and said second oligonucleotide each comprise at least eight consecutive 2'-hydroxyl ribonucleotides.

199. (New) The method of claim 184, wherein each of said first and said second oligonucleotides are about 17 to about 20 nucleoside subunits in length.

200. (New) The method of claim 199, wherein each of said first and said second oligonucleotides are 17 subunits in length.

201. (New) The method of claim 199, wherein each of said first and said second oligonucleotides are 20 subunits in length.